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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/671,764	09/27/2000	Joseph R. Pisegna	M-8978 US	7433

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 02/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/671,764	PISEGNA ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-10,20-29 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-10, 20-29 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-4, 6-10, 20-29 and 31 are pending.

Applicants' amendment filed November 17, 2004 is acknowledged, and applicants' response has been fully considered. Claim 1 has been amended. Therefore, claims 1-4, 6-10, 20-29 and 31 are examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-4, 6-10, 20-29 and 31 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for a method of increasing the efficacy of a gastric H^+/K^+-ATPase inhibitor (PPI) in a human in need of a PPI by administering an effective amount (e.g., 0.1-10 mg/kg/hr) of a pentagastrin, a gastrin or a gastrin analog in conjunction with the PPI, or a kit for the treatment of pathology characterized by excess gastric acid secretion, comprising a container containing a PPI, and a container containing a pentagastrin, a gastrin or a gastrin analog because the specification only discloses cursory conclusions without data supporting the findings, which state that the present invention provides a method of treating pathological conditions characterized by excess gastric acid secretion, in particular the method of administering a gastrin, a pentagastrin or an analog thereof in

conjunction of a PPI, which will result in increased efficacy, or a kit for the treatment of pathology characterized by excess gastric acid secretion, comprising a container containing a PPI and a container containing pentagastrin (page 2, line 7-page 4, line 2). However, there are no indicia that the present application enables the full scope of the claim in view of a method of increasing the efficacy of a PPI in mammal and a kit for the treatment of pathology of excess gastric acid secretion as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence or absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding analogs of gastrin or pentagastrin, and PPIs, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

There are no working examples indicating the claimed methods in association with the variants except for administering pantoprazole to humans having pentagastrin (1 μg/kg/hr) - induced gastric acid secretion and monitoring the effect of pantoprazole in the inhibition of pentagastrin-induced gastric acid secretion (Example 1).

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., Simon *et al.* , Aliment. Pharmacol. Therap. 4, 239-245 (1990)) indicates the effect of a PPI, BY1023/SK&F 96022 on the pentagastrin-stimulated acid secretion in healthy male volunteers; Murphy *et al.* (U. S. Patent 4,997,950) teach the use of analogs from C-terminus of gastrin in adjunctive therapy with a PPI, omerprazole in animal models. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide teachings on administering an effective amount (e.g., 0.1-10 mg/kg/hr) of a pentagastrin, a gastrin or a gastrin analog in conjunction with a PPI, and the effect of the gastrin or pentagastrin peptide in increasing the efficacy of the PPI in a human to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a method of increasing the efficacy of a PPI in a human in need of a PPI by administering an effective amount of a gastrin, a pentagastrin or a gastrin analog in conjunction with the PPI, or a kit for the treatment of pathology of excess gastric acid secretion, comprising a PPI and a gastrin, a pentagastrin or a gastrin analog, however, the in vivo effects of using an effective amount of gastrin, pentagastrin or a gastrin analog to increase the efficacy of a PPI are not adequately described or demonstrated in the specification, e.g., the specification indicates pentagastrin is an agent that is typically to increase acid secretion (page 2, lines 9-10), and PPIs are potent inhibitors of gastric acid secretion by inhibiting H^+/K^+-ATPase (page 2, lines 1-5), furthermore, Example 1 also indicates pentagastrin (1 μg/kg/hr) is administered continuously to induce hypersecretion in healthy subjects, and single doses of *i.v.* pantoprazole ranging 20-120 mg are found to suppress gastric acid secretion in a dose-dependent manner.

However, the specification has not demonstrated an effective amount of pentagastrin such as 0.1-10 mg/kg/hr increases the efficacy of PPI in inhibiting gastric acid secretion as compared to the activity of using PPI alone, and there is no reference point for comparison. Since pentagastrin also induce gastric acid secretion aside from increasing efficacy of PPI in a human, the effect of pentagastrin in the combination therapy is unpredictable.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of increasing the efficacy of a PPI in mammal by administering a gastrin, a pentagastrin, or an analog of gastrin in conjunction with the PPI, or a kit for the treatment of pathology of excess gastric acid secretion, comprising a PPI and gastrin, or an analog of gastrin or pentagastrin. The specification indicates the pentagastrin can be administered before, simultaneously with or after the PPI administration with the general dosages (0.1-10 mg/kg/hr) for pentagastrin, gastrin, or analogs thereof (page 2), and Example 1 demonstrates single doses of *i.v.* pantoprazole ranging 20-120 mg suppressed gastric acid secretion in a dose-dependent manner in healthy subjects under continuous pentagastrin (1 μg/kg/hr) -induced hypersecretion. However, the specification has not demonstrated an effective amount (0.1-10 mg/kg/hr) of a gastrin, a pentagastrin, or an analog of gastrin increases the efficacy of a PPI as compared to the activity of PPI alone since there is no reference point for comparison. Moreover, there are no working examples indicating the effects of gastrin, pentagastrin, or an analog thereof in increasing the efficacy of various PPIs in a human. Because pentagastrin has also an effect of inducing gastric acid secretion other than increasing efficacy of PPI, it is unpredictable about the effect of pentagastrin on gastric acid secretion in combination

therapy. Since the specification fails to provide sufficient teachings on the use of gastrin, pentagastrin or various analogs thereof in conjunction with a PPI, and the in vivo effects of these peptides in increasing efficacy of PPI and inducing gastric acid secretion, it is necessary to carry out undue experimentation to assess the effects of gastrin, pentagastrin or various analogs thereof in the claimed method.

(6). Nature of the Invention

The scope of the claims encompasses a method of increasing the efficacy of a PPI in a human in need of a PPI by administering a gastrin, a pentagastrin or an analog thereof in conjunction with the PPI, but the specification has not provide sufficient teachings, nor has demonstrated using an effective amount of the peptide in conjunction with a PPI in the claimed method. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed methods, the effect of the variant is unpredictable, and the teaching in the specification is limited, therefore, it is necessary to carry out further experimentation to assess the effects of using a gastrin, a pentagastrin or various gastrin analogs in the method of increasing efficacy of various PPIs.

In response, applicants provides a post filing reference (Bardan et al. (2004) Supplement to Gastroenterology, 1244): Suppl. 2, Abstract M1439, designated Exhibit A), which indicates that prestimulation of gastric proton pumps with oral PG (pentagastrin) enhances the inhibitorv effect of omeprazole (a PPI) on acid secretion. This effect is mediated by a local effect of PG. Co-administraton of PG and omeprazole may be used clinically to potentiate the therapeutic effect of omeprazole. This published scientific literature thus clearly establishes that pentagastrin

can be used in either a pre-stimulatory mode or coadministered with a PPI to enhance the activity of that PPI. Moreover, the scientific literature further establishes that the effect is clinically relevant. The claimed methods clearly work and indeed, have clinical value. In view of this showing no undue experimentation is required to practice the claimed invention. (pages 5-6 of the response).

The response has been fully considered, however, the argument is not found persuasive because the specification only demonstrates pentagastrin at 1 μg/kg/hr is administered continuously to induce hypersecretion in healthy subjects as a model for patients with Zollinger-Ellison Syndrome, and single doses of *i.v.* pantoprazole ranging 20-120 mg are found to suppress gastric acid secretion in a dose-dependent manner, and there are no working examples indicating pentagastrin increased the efficacy of PPI in a human since there is no reference point for comparison (i.e., administering PPI only), thus the specification has not provided sufficient teachings for the claimed method. Regarding the post filing reference (Bardan et al. (2004)), the document does not refer any of applicant's publications, and it does not clearly follow the "teachings" of instant application (see *In re Lundberg* 117 USPQ 190). While the post filing reference teaches the co-administration of oral pentagastrin and omeprazole to rats (non-ligated and pylorus-ligated) significantly increases gastric pH level as compared to omeprazole only, and indicates co-administration of pentagastrin and omeprazole may be used clinically to potentiate the therapeutic effect of omeprazole, it does not describe the effects of pentagastrin, gastrin or analogs thereof in enhancing the efficacy of various PPIs in a human having a disorder of excess gastric acid secretion, which requires undue experimentation to assess the effect of a

gastrin analog on the efficacy of a PPI in the combination therapy. Therefore, the rejection remains.

Conclusion

3. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached at 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D. CMK
Patent Examiner

JON WEBER
SUPERVISORY PATENT EXAMINER

CMK
January 28, 2005